

REMARKS

Claim Amendment

Claim 1 has been amended to specifically recite particular receptors on a T cell that are encompassed by the present invention and thereby clarify the present invention. Support for this amendment is found in the specification on page 11, lines 19-22, for example. This amendment merely places the claims in a condition for allowance or reduces the issues for appeal and therefore, Applicants respectfully request that the amendment be entered.

Rejection of Claims 1, 9-11, 18, 19, 24, 25, 27, 28, and 31-35 Under 35 U.S.C. § 102(b):

The Examiner has maintained the rejection of Claims 1, 9-11, 18, 19, 24, 25, 27, 28 and 31-35 under 35 U.S.C. § 102(b), contending that these claims are anticipated by Lobb et al. (U.S. Patent No. 5,871,734), as evidenced by Arrhenius et al. (U.S. Patent No. 5,869,448) and Sato et al. The Examiner contends that Lobb et al. teach the use of an antibody against VLA-4 to treat asthma. The Examiner asserts that it is an inherent property of anti-VLA-4 that it would prevent VLA-4 mediated T cell activation. With regard to Applicants' prior response, the Examiner replies that Lobb et al. indicate that anti-VLA-4 "may attenuate signal transduction necessary for the release of inflammatory mediators and/or cell chemotactic agents", and that Sato et al. confirms that it is an inherent property of certain anti-VLA-4 mabs that they prevent T cell activation (Fig. 1) and that mitogenic VLA-4 antibodies require solid phase crosslinking. Therefore, the Examiner asserts that it is an inherent property of the antibodies taught by Lobb et al. that they would prevent T cell activation.

Applicants traverse the Examiner's rejection of 1, 9-11, 18, 19, 24, 25, 27, 28 and 31-35 under 35 U.S.C. § 102(b). Initially, in order to clarify the claims and expedite prosecution, Applicants have amended Claim 1 to clarify that the antibody used in the present invention is an antibody selected from an antibody to a T cell antigen receptor (TCR), CD3, CD8 or CD4. Lobb et al. do not teach or suggest the use of an antibody against any of these receptors, and therefore, Lobb et al. do not anticipate the claimed invention.

To further address the Examiner's comments under this section as they might be applied in the § 103 rejection below, Applicants submit that the statement that anti-VLA-4 "may attenuate signal transduction necessary for the release of inflammatory mediators and/or cell chemotactic

agents" does not specifically indicate that anti-VLA-4 is capable of inducing inactivation of a T cell. Rather, taken in the context of that passage of Lobb et al., the statement is referring to a reduction in the ability of *leukocytes* to release inflammatory mediators and chemotactic agents (which include not only lymphocytes, but also eosinophils and neutrophils - see col. 2, lines 49-65; Example 1, col. 12, lines 8-22 with Fig. 4., and Example 2, col. 13, lines 4-7). This statement does not necessarily specifically refer to an induction of T cell *inactivation*. Indeed, referring to Figs. 4A-4D and Example 1, col. 12, lines 8-22, taken together with Example 2, col. 13, lines 4-7, it appears that administration of anti-VLA-4 only decreased the percentage of eosinophils and neutrophils and actually increased the percentage of lymphocytes over time.

Moreover, with regard to Sato et al., the experiment illustrated by Fig. 1 of that reference shows that binding of certain epitopes of VLA-4 in combination with the binding of CD3 by anti-CD3 resulted in greater T cell activation than other VLA-4 epitopes. Moreover, Applicants do not dispute that under some conditions, VLA-4 can act as a costimulatory molecule, as shown by Sato et al. in conjunction with CD3. The experiment in Sato et al. also shows that anti-VLA-4 alone is incapable of *stimulating* T cell activation without the additional stimulation through CD3 (see page 2941, first full paragraph). Applicants wish to point out, however, that the inability of anti-VLA-4 to induce T cell activation is not the same as *preventing* activation or *inducing inactivation* of a T cell (i.e., there was no prevention of activation demonstrated in Sato et al., just insufficient signal provided by VLA-4 alone to achieve activation).

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1, 9-11, 18, 19, 24, 25, 27, 28 and 31-35 under 35 U.S.C. § 102(b).

Rejection of Claims 1-3 and 9-35 Under 35 U.S.C. § 103:

The Examiner has maintained the rejection of Claims 1-3 and 19-35 under 35 U.S.C. § 103, contending that these claims are unpatentable over Lobb et al. as evidenced by Arrhenius et al. in view of Schramm et al. The Examiner contends that Lobb et al. teach an antibody that binds to a receptor on a T cell and causes the depletion or inactivation of a T cell for the reasons of record and the reasons set forth above under 35 U.S.C. § 102. The Examiner acknowledges that Lobb et al. do not teach the use of anti-TCR $\alpha\beta$ antibodies, but contends that it would have been *prima facie* obvious to have created the invention because Lobb et al. teaches the aerosol administration of an

antibody to treat asthma, and because Schramm et al. allegedly teach the use of intravenous anti-TCR $\alpha\beta$ antibodies can treat asthma. The Examiner asserts that motivation is provided because Lobb et al. teach that the anti-T cell antibody can be administered by a variety of methods including aerosol. The Examiner further contends that because Lobb et al. teach that anti-VLA-4 antibodies administered by aerosol treat asthma and because Schramm et al. teach that anti-TCR $\alpha\beta$ antibodies administered intravenously treat asthma, and finally because both antibodies bind T cells, there is an expectation of success at making the claimed invention. The Examiner also contends that Applicants' discuss of Fahy et al. is irrelevant because the antibody of Fahy et al. does not bind to a T cell. Finally, the Examiner further asserts that Applicants have made a plethora of statements regarding the effects of the claimed invention without evidence to support the statements.

Applicants again traverse the Examiner's rejection of Claims 1-3 and 9-35 under 35 U.S.C. § 103. Applicants submit that a *prima facie* case of obviousness has not been established.

First, the combination of references fails to teach each and every element of the claimed invention because none of the reference teach or suggest the use of an aerosolized antibody that meets the limitations of binding to the presently recited receptor on a T cell and causing the depletion or inactivation of the T cell. Lobb et al. teach an aerosolized VLA-4 antibody, but this is not an antibody that binds to any of the currently recited receptors. Schramm et al. do not teach an aerosolized antibody. Arrhenius teaches a cyclic peptide that inhibits binding between VLA-4 and integrin and excludes the use of antibodies to inhibit such interaction (see col. 5, lines 5-15), and therefore does not teach the use of any antibody at all. Therefore, the combination fails to teach or suggest each and every element of the claimed invention.

Second, with regard to the motivation to arrive at the claimed invention, Applicants first submit that even if Lobb et al. teach that anti-VLA-4 can be administered by a variety of routes, this is not sufficient to motivate one of skill in the art to administer any other antibody by a variety of routes. VLA-4 and the claimed T cell receptors are completely different receptors, and Lobb et al. provide absolutely no suggestion to use an antibody to a different receptor. Similarly, Schramm et al. provide no suggestion to administer the anti-TCR $\alpha\beta$ antibody by aerosol. In addition, while VLA-4 is found on leukocytes other than lymphocytes (e.g., see Lobb et al., col. 2, lines 60-61), the claimed receptors are all *T cell-specific*, and therefore, one would not be motivated to extrapolate the results achieved by effecting a receptor found on a variety of cell types to a different receptor

found on only one cell type. Furthermore, as taught in the specification, prior to the present invention, it was thought that antibodies delivered by aerosol must be administered in high doses to overcome the effects of expected low potency and to successfully reach the target airways (see page 10, lines 22-26, including the reference to both Fahy et al. and U.S. Patent No. 6,165, 463), which would dissuade one of skill in the art to look to aerosol delivery for the antibody of Schramm et al.

With regard to Applicants' prior arguments regarding the experiments of Fahy et al., contrary to the Examiner's contention, Applicants submit that these arguments are directly relevant to the Examiner's stated rejection regarding the motivation to combine the references. Specifically, the Examiner bases motivation for combining Lobb et al. and Schramm et al. at least in part on the argument that even though one reference teaches aerosol administration of an antibody (Lobb) and one reference teaches systemic administration of a different antibody (Schramm), both references teach the use of an antibody that binds to the same cell type and that administration of the antibody treats asthma, and therefore it would be expected that the antibody of Schramm et al. would treat asthma even if administered by aerosol. Applicants' argument directly rebuts this line of reasoning because it shows, using the experiment of Fahy et al. as an example, that provision of a therapeutic effect by administration of antibodies systemically does not necessarily mean that the same effect will be provided when the same antibody is administered by aerosol. Indeed, as discussed on page 5, lines 10-16, Fahy et al. used aerosolized anti-IgE to test whether direct delivery of the antibody to the airway would have the same effect as the systemic delivery of the antibody, which had already been shown to attenuate early and late phase responses to inhaled allergen (Fahy et al., 1999, *Am. J. Respir. Crit. Care Med.* **160**:1023-1027). Fahy's experiment demonstrated that the aerosolized anti-IgE did not attenuate the airway responses to inhaled allergen and in at least one subject, the antibody proved to be immunogenic. Therefore, this experiment shows that, based on the art, one can not assume that achievement of a therapeutic effect by administration of an antibody systemically can be extrapolated to aerosol administration of the same antibody. The argument can be taken a step further in that the Examiner has taken attempted to compare two completely different antibodies on this basis, which makes prediction of effects even more unreasonable. Therefore, the Examiner's argument that one can take the results of Lobb et al. and thereby predict a result using the antibody of Schramm et al. is not fairly based on scientific evidence.

Moreover, Applicants submit that there is no motivation provided by any of the cited references to substitute the anti-VLA-4 antibody of Lobb et al. for the anti-TCR $\alpha\beta$ antibody of Schramm et al., or *vice versa*. Neither reference attempts to extend its teachings beyond the specific antibody. VLA-4 and the claimed T cell receptors are completely different receptors, such that antibodies that bind to the receptors will have different effects on the T cell. "A statement that modifications of the prior art to meet the claim limitations would have been 'well within the ordinary skill of the art' at the time the invention was made', because the cited references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993)." MPEP 2143.01.

Third, there is no expectation of success provided by the combination of references at being able to make and use the claimed invention. As discussed previously, Applicants submit that the Examiner has not provided sufficient evidence that one can make predictions regarding the presently recited T cell-specific antibodies on the basis of any action shown for antibodies against VLA-4, which is found on many different cell types. As argued previously, Lobb et al. can not provide any expectation of success of using any other type of treatment for asthma than the one specifically taught in that patent, which is via regulation of VLA-4. Schramm et al. can not provide any expectation of success at using aerosolized administration of an antibody because the reference is not directed to aerosol administration. The combination of references fails to provide an expectation of success because there is no teaching or suggestion of administration of an aerosolized antibody as claimed.

Finally, with regard to the Examiner's contention that Applicants have made a number of statements regarding advantages of the invention without providing evidence in support of the statements, Applicants disagree. The evidence supporting Applicants' statements regarding the advantages of the invention is clearly provided in the specification.

For example, Applicants have submitted that the claimed method targets pulmonary T cell populations in the absence of any substantial effect on peripheral T cells, which is a large advantage over previously described methods (e.g., the method of Schramm et al.), which target T cell responses systemically. The present invention targets pulmonary T cell populations because the antibody is administered to the lung (i.e., the pulmonary tissue). Example 5 and Fig. 3 of the

specification provide evidence by working example that the claimed method targets pulmonary T cell populations in the absence of any substantial effect on peripheral T cells, in contrast to systemic administration, which effected pulmonary and peripheral T cells.

Additionally, in contrast reports of the administration of other aerosolized antibodies (e.g., anti-IgE administration, described by Fahy et al. (1999, *Am. J. Respir. Crit. Care Med.* **160**:1023-1027)), the present inventors have demonstrated that the claimed method is highly effective at reducing airway hyperresponsiveness. This is demonstrated in all of the examples.

Another advantage of targeting T cells expressing a $\gamma\delta$ T cell receptor that are present at the allergic site by the localized administration method of the present invention reduces allergic inflammation-associated exacerbation of AHR without affecting the adaptive immune system. $\gamma\delta$ T cells are generally not considered to be part of the adaptive immune system (i.e., antigen-specific immune mechanisms, which include $\alpha\beta$ TCRs) because they have not been readily linked to antigen-specific responses (**provide citation here**). Therefore, selective targeting of $\gamma\delta$ T cells for depletion has the advantage of not targeting cells that participate in the adaptive immune response (e.g., $\alpha\beta$ T cells or B cells). Examples of selective targeting of $\gamma\delta$ T cells is shown in Examples 2-6.

Finally, in contrast to the evidence and assertions generally in the art that antibodies delivered by aerosol must be administered in high doses to overcome the effects of expected low potency and to successfully reach the target airways, the method of the present invention is effective at extremely *low* doses of antibody. Indeed, the method of the present invention achieves efficacy with antibody doses that are believed to be about *1000-fold* or more lower than systemic doses of antibody required to achieve the same effect. This is demonstrated in Example 5 and Fig. 1 and is further explained on page 34, line 9 to page 35, line 6.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1-3 and 19-35 under 35 U.S.C. § 103.

Applicants have attempted to address all of the Examiner's concerns as set forth in the July 17 Office Action and submit that the claims are in a condition for allowance. In the event that the Examiner has any further questions or concerns regarding the claims, he is encouraged to contact the below-named agent at (303) 863-9700.

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